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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 03/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/798,169	LATIF, ZUHAIR A.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim 1-7 are pending in the application and under current examination.

Priority

Applicant's claim for the benefit of a prior-filed application 10/654,723 and 60/409,305 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. [1] as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 10/654,723, filed September 2003 is drawn to a different subject matter, namely transferring an specific immune response into a cloned animal via adoptive transfer of lymphocytes of the founder mammal, whereas instant disclosure is drawn to cloning a mammal from lymphocytes of the founder mammal. As such, the disclosure of the prior-filed application fails to provide adequate support in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. This application

does not qualify as a continuation of U.S. Application No. 10/654,723. The priority date for the instant claimed invention has been established as the filing date of this application, i.e. March 11, 2004. Appropriate amendment of the specification is required.

Otherwise, Applicant is invited to point to specific passages of the priority document, where the support for instantly claimed subject matter can be found.

Specification

The disclosure is objected to because of the following informalities: paragraph 0001 contains blank spaces. Appropriate correction is required.

Claim Objections

Claim 4 is objected to because a splenocyte is not considered a lymphocyte in the pertinent art.

Claims 1-7 are objected to because they inconsistently and interchangeably use the term "animal" and "mammal".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the nature of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claims are drawn to a method of creating an immune response in a clone that is identical to that of a founder mammal, wherein the clone is obtained through somatic nuclear cloning using isolated lymphocytes of an immunized founder animal as the nuclear donor, and allowing the clone to develop to maturity such it develops identical immune response of said founder, wherein the animal is selected from the group consisting of mice, rabbits, sheep, horses, etc.

To successfully practice the invention without undue experimentation, it requires 1). Cloning an animal from lymphocytes had been a routine procedure in the art; and 2). The cloned animal is capable of providing *identical* immune response of the founder.

Lymphocyte nuclear transfer cloning was not routine in the art at the time of filing, and the specification fails to provide sufficient guidance for lymphocyte NT.

The specification outlines a general protocol for cloning (e.g. fig. 1), and refers to textbook and prior art publications for its practice. The specification contains a hypothetical example, contemplates using B lymphocyte of a FTT transgenic mice immunized with a T4-TG antigen as donor nuclear material to construct a clone. However, the specification is complete silent with regard to the state of the art in animal cloning, particularly somatic nuclear transfer with nuclear material of lymphocytes in large animals; and the specification is complete silent concerning the immune state of the cloned mammal compared to the founder mammal, and whether indeed an identical immune response of the founder could be reproduced in its cloned offspring.

Turning to the state of the art, at around time of instant filing, reproductive cloning is still in its infant stage, and extremely inefficient. Such inefficiency often reflects the real difficulty and challenge in animal cloning. *Yanagimachi* (Mol Cell Endocrinol 2002;187:241-8) teaches, "CLONING EFFICIENCY-AS DETERMINED BY THE PROPORTION OF LIVE OFFSPRING DEVELOPED FROM ALL OOCYTES THAT RECEIVED DONOR CELL NUCLEI-IS LOW REGARDLESS OF THE CELL TYPE (INCLUDING, EMBRYONIC STEM CELLS) AND ANIMAL SPECIES USED. IN ALL ANIMALS EXCEPT OF JAPANESE BLACK BEEF CATTLE, THE VAST MAJORITY OF CLONED EMBRYOS PERISH BEFORE REACHING FULL TERM" (Abstract), and "THUS FAR, CLONED OFFSPRING

THAT SURVIVED BIRTH AND REACHED ADULTHOOD WERE THE EXCEPTION RATHER THAN THE RULE (page 243, left column, emphasis added). *Yanagimachi* goes on to teach, "THIS LOW EFFICIENCY OF CLONING SEEMS TO BE DUE LARGELY TO FAULTY EPIGENETIC REPROGRAMMING OF DONOR CELL NUCLEI AFTER TRANSFER INTO RECIPIENT OOCYTES. CLONED EMBRYOS WITH MAJOR EPIGENETIC ERRORS DIE BEFORE OR SOON AFTER IMPLANTATION" (abstract). *Wells et al* (Trends Biotechnol 2003:21:428-32) teach that the continuous loss of clones throughout pregnancy and high mortality during the perinatal period raise serious animal welfare concerns and these losses can mostly be attributed to faulty epigenetic reprogramming of the donor cell genome, resulting in major dysregulation of gene expression (paragraph bridging left & right column in page 1). Clearly, the state of the art has not reach the level of routine experimentation in NT cloning of animals.

As to the state of the art concerning nuclear cloning with lymphocyte nuclear material, lymphocytes are differentiated cells, when used as donor nucleus material, nuclear totipotency has to be reestablished by erasing epigenetic constraints imposed on the donor genome during differentiation in a process which involves active chromatin remodeling. To this end, the skilled artisan teaches many different donor cell types and cell cycle combinations have been investigated and proven to be capable of generating cloned offspring, but lymphocyte was not one of such cells. For example, *Oback and Wells* (Cloning & Stem Cells 2002;4:147-68) teach only mouse lymphocytes have been investigated, 1.8% reconstructed oocytes developed to the stage of blastocyst, none developed to the stage for implantation (table 1).

A publication of *Hochedlinger et al* provides further insight. To overcome the art known hurdle of lymphocyte nuclear cloning, *Hochedlinger et al* (Nat 2002;415:1035-8)

used a different approach, a two-step cloning procedure (e.g. abstract). They reasoned since embryonic stem cell is much more effective for reprogramming, they first established ES cells from balstocysts developed from oocytes having a lymphocyte nuclear material, and then injected the ES cells into tetraploid blastocysts to generate monoclonal mice. Thus the generated mice are derived from ES cells rather then a somatic cell. Even so, they reported the efficiency was about ten times lower than that from other donor cell populations, and teach, [the inefficiency] "MIGHT BE DUE TO INEFFICIENT REPROGRAMMING OF THE LYMPHOCYTE GENOME OR DIFFERENCES IN THE SENSITIVITY OF THE LYMPHOCYTE NUCLEI TO THE NUCLEAR TRANSFER PROTOCOL" (column 2, page 1035). *Hochedlinger et al* go on to teach, "THE TWO-STEP APPROACH USED TO PRODUCE THE MONOCLONAL MICE DOES NOT DEMONSTRATE THAT B- ANDT-CELL NUCLEI CAN BE DIRECTLY REPROGRAMMED TO GENERATE THE EXTRA-EMBRYONIC LINEAGES" (emphasis added), and "THE EPIGENETIC STATE OF THE GNES CRUCIAL FOR EMBRYONIC DEVELOPMENT IN THE TERMINALLY DIFFERENTIATED LYMPHOCYTE NUCLEUS MAY BE IN A CONFORMATION THAT CANNOT OR CAN ONLY RARELY BE REPROGRAMMED ON TRANSFER INTO THE OOCYTE" (paragraph bridging pages 1037-8). Clearly, lymphocytes are extremely difficult to clone, and the possibility of cloning large mammals from lymphocyte is yet to be seen at the time.

Lymphocyte NT cloning in large mammals has not proven possible

Claims encompass cloning any mammalian species and preferably a horse. *Wilmut* (Cloning Stem Cell 2003;5:99-100) teaches, "BY THE TIME OF DOLLY'S DEATH IN 2003, CLONES HAD BEEN DERIVED FROM ADULT CELLS OF SEVERN MAMMALIAN SPECIES, BUT THE SAME TECHNIQUES WERE NOT SUCCESSFUL IN SEVEN OTHERS, DESPITE INTENSIVE EFFORTS BY

EXPERIENCED RESEARCH TEAMS. THESE INCLUDE RHESUS MONKEY, RAT, DOG, AND HORSE. THIS FAILURE EMPHASIZES THE IMPORTANCE OF DIFFERENTCES BETWEEN SPECIES. THE DIFFERENCE MIGHT BE IN THE MOLECULAR MECHANISMS THAT REGULATE EARLY DEVELOPMENT OR IN ENABLING TECHNIQUES FOR OOCYTE RECOVERY, EMBRYO CULTURE, OR EMBRYO TRANSFER. SUCH DIFFERENCES HAVE ALREADY BEEN IDENTIFIED BETWEEN THE SPECIES FROM WHICH CLONES HAVE BEEN DERIVED". Clearly, neither the state of the art nor specification provides enablement for cloning a horse, and thus the specification fails to provide support for the full scope of the invention.

As to cloning animals by lymphocyte NT method, the only known success was the publications of *Oback and Wells,* showing a two-step method in the mouse. It is noted the two-step method could not have been used in cloning large animals, because ES cell has yet to be identified in animals other than the mouse (See *Pera et al.* **Journal of Cell Science** 113: 5-10, 2000), *Pera et al* present the generic criteria for pluripotent ES or EG cells [see p. 6, 2nd column] and state that, "THUS FAR, ONLY MOUSE EG OR ES CELLS MEET THESE GENERIC CRITERIA. PRIMATE ES CELLS MEET THE FIRST THREE OF THE FOUR CRITERIA, BUT NOT THE LAST. NUMEROUS OTHER CANDIDATE MAMMALIAN ES CELLS HAVE BEEN DESCRIBED OVER THE YEARS IN DOMESTIC AND LABORATORY SPECIES, BUT ONLY IN THE MOUSE HAVE ALL CRITERIA BEEN MET RIGOROUSLY." [See p. 6, 2nd column, last paragraph]. In view of such, the invention does not appear to be enabled for lymphocyte NT cloning of large animals in the absence of clarification of the contradictory evidence found in the references.

The cloned offspring appears to be incapable of providing an identical immune response of the founder.

As to the question of whether a cloned mammal obtained from a lymphocyte nuclear transfer cloning is capable of developing *identical* immune response of the founder animal, although the nuclear donor and clone will have the same karyotype or chromosomal number, the clone and the donor are unlikely to have the same or identical nucleotide sequence because during DNA replication there more likely than not will be some nucleotide changes particularly considering that lymphocytes are known to have high mutation rates. The specification is complete silent concerning the immune state of the cloned mammal compared to the founder mammal, and whether indeed an identical immune response of the founder could be reproduced in its cloned offspring.

To this end, the study of *Hochedlinger et al* again provides insight. Taking the monoclonal mouse as an example, *Hochedlinger et al* reported the immunoglobulin alleles of the starting ES cells have been rearranged by deletional joining and inversional joining (column 2, 3rd paragraph) during the first step of cloning, i.e. while establishing the ES cells from the blastocyte, which was developed from oocytes having the founder lymphocyte nuclear material. Subsequently, the cloned offspring carries rearranged Ig alleles, which differ from the original B lymphocyte of the founder. Moreover, the Ig alleles of the clone are only similar to *one* B-lymphocyte, while the founder has a reservoir of lymphocytes with diverse Ig alleles and antigen specificities, the monoclonal mice thus could only simulate one aspect of the founder immune response, it cannot provide an identical immune response as that of the founder upon

immunization at their maturity because the founder and the clone do not share the same lymphocyte reservoir.

Lymphocytes are the only cells in the body that express highly diverse antigen receptors and secrete highly diverse antibodies that recognize a wide variety of foreign substances. This diversity is generated during the lifetime of a mammal via maturation of lymphocytes from precursor cells (which cannot respond to antigens). Responding to various antigens, an individual is capable of making a tremendous number of structurally distinct antibodies, and T cell receptors, estimated at up to 10^9, each with a distinct structure and binding specificity. Creating an identical immune response of the founder in an offspring requires at least similar, if not identical, Ig and T cell receptor repertoire of the offspring compared to the founder. This collection of antibody and T cell repertoire is not inherited but requires exposure to various antigens, through lymphocyte maturation and activation processes, which processes include random somatic gene recombination of a limited set of inherited germline DNA sequences into functional genes that encode the V regions of heavy and light chains of Ig superfamily proteins, as well as random addition of nontemplate nucleotide sequences to these V segment genes (See e.g. selected excerpts from *Cellular and Molecular Immunology*, Ed. Abbas et al, 2000); wherein the random somatic gene recombination involves complex mechanism of V(D)J Ig gene recombination, somatic hypermutation, gene conversion, and class switch (*Ollila et al*, Intl J Biochem Cell Biol 2005;37:518-23). From the experiment of *Hochedlinger et al*, such diversity did not pass to the offspring, only the lymphocyte that provided the nuclear material was reproduced with some allele

rearrangements. Clearly, a cloned offspring normally would not have the same cellular and humoral immune repertoires compared to the founder animal and thus is incapable of providing an identical immune response as that of the founder. As such, the claimed invention does not appear to be enabled in the absence of clear and convincing evidence to the contrary.

Further, the potential effects of cloning on genetic and epigenetic aspects of cloned offspring remain largely unknown, and remarkable differences between the founder and its clone have been reported in both somatic and embryonic cell nuclear transfer cloning.

Since, except the mouse, the embryonic stem cells for remain mammals recited in claim 2 have yet to be identified, they have to be cloned from somatic cells. A variety of phenotypes and epigenetic alterations have been reported in animals cloned from somatic cells, and the exact nature and consequences of the alterations remain unclear (*Ogura et al*, Cloning and Stem Cells 2002;4:397-405, e.g. the abstract). *Ogura et al* teach even for those mice that were viable at birth and appear to be normal, they died earlier than the genotype-matched controls, "MOST PROBABLY DUE TO SEVERE PNEUMONIA, WHICH INDICATES THAT UNEXPECTED PHENOTYPES CAN APPEAR AS A RESULT OF THE LONG-TERM EFFECTS OF SOMATIC CELL CLONING" (abstract). *Tamashiro et al* (Nat Med 2002;8:262-7) echo such conclusion, and teach, "ALTHOUGH FULL-TERM DEVELOPMENT OF ANIMALS CLONED FROM ADULT SOMATIC CELLS HAS BEEN REPORTED, PROBLEMS IN THE RESULTING PROGENY INDICATE THAT THE CLONING PROCEDURE MAY NOT PRODUCE ANIMALS THAT ARE PHENOTYPICALLY IDENTICAL TO THEIR CELL DONOR" (abstract). *Dr. Wilmut*, a pioneer in animal cloning, teaches "THE MOST STRIKING THING ABOUT THE TECHNIQUES THAT EMERGED DURING DOLLY'S LIFE IS THAT

MAMMALIAN CLONING REMAINS A REPEATABLE, BUT INEFFICIENT PROCEDURE. IT IS STILL TRUE THAT ONLY 1-5% OF RECONSTRUCTED EMBRYOS DEVELOP TO BECOME VIABLE OFFSPRING, REGARDLESS OF VARIATIONS IN SPECIES, CELL TYPE, OR NUCLEAR TRANSFER PROTOCOL. THIS LOW OVERAL SUCCESS RATE IS THE CUMULATIVE EFFECT OF FAILURE AT ALL STAGES OF DEVELOPMENT, INCLUDING AFTER BIRTH. AN EXTRAORDINARY VARIATIY OF ABNORMALITIES HAVE BEEN DESCRIBED IN CLONED FETUSES AND OFFSPRING." And "THIS OUTCOME HAS BEEN ASSOCIATED WITH VERY GREAT VARIATION IN GENE EXPRESSION IN CLONED EMBRYOS, FETUSES, AND OFFSPRING" (Cloning Stem Cells 2003;5:99-10, see mid-section of column 2, page 99, emphasis added). Through pathological studies of a group of lambs that were not viable after birth, *Rhind et al* (Nat Biotech 2003;21:744-5) offered an alternative view contrary to the opinion that the majority of cloned animals are 'seemly healthy'. *Rhind et al* teach, "MORE SUBTLE EXPRESSION OF THE DEFECTS COULD BE PRESENT IN SURVIVING CLONES THAT ARE APPARENTLY NORMAL", and "BY REVEALING REPEATED PHENOTYPIC ABNORMALITIES THAT HAVE NOT BEEN PREVIOUSLY RECOGNIZED IN LAMBS GENERATED WITH NUCLEAR TRANSFER TECHNOLOGY, OUR SURVEY REVEALS THE NEED FOR DETAILED PATHOLOGICAL INVESTIGATION OF CLONED ANIMALS THAT FAIL" (paragraph bridging columns 1 & 2, page 745). *Smith and Murphy* (Cloning Stem Cells 2004;6:126-32) point to the underlying reasoning why genetic and epigenetic variations occurred, i.e. the mechanism about how the host cytoplasm and donor nuclei interact to produce a developmentally competent reconstructed embryo is largely unknown. *Smith and Murphy* teach, apart from the major chromosomal anomalies found in developmentally arrested embryos and fetuses, less detrimental rearrangements and/or mutations are likely to go unnoticed in most donor cell karyotypes, which could lead to inheritable anomalies among clones and their offspring. *Smith and Murphy* go on

to teach that the variations may come from the donor nuclear DNA sequence, the mitochondrial DNA from the host oocyte, and epigenetic alterations to the DNA or to the histone packaging proteins.

Even when cloning using ES cells, epigenetic instability may lead to genotype variations. *Humpherys et al* (Science 2001;293:95-7) teach variation in imprinted gene expression was observed in most cloned mice, even in those derived from ES cells of the same subclone. "THESE DATA IMPLY THAT EVEN APPARENTLY NORMAL CLONED ANIMALS MAY HAVE SUBTLE ABNORMALITIES IN GENE EXPRESSION" (abstract). The claimed invention encompasses cloning primates including human being, *Simerly et al* (Science 2003;300:297) report the molecular obstacles in cloning primates, and concludes, "PRIMATE NUCLEAR TRANSFER APPEARS TO BE CHALLENGED BY STRICTER MOLECULAR REQUIREMENTS FOR MITOTIC SPINDLE ASSEMBLY THAN IN OTHER MAMMALS", AND "WITH CURRENT APPROACHES, NT TO PRODUCE EMBRYONIC STEM CELLS IN NONHUMAN PRIMATES MAY PROVE DIFFICULT—AND REPRODUCTIVE CLONING UNACHIEVABLE". Apparently, it was not and has yet to become routine in the art to obtain genotypically and phenotypically identical mammals, and it has yet to be achieved to clone primates.

While, the intent for citing the references is not to say that a substantially the same immune response can never be achieved in a cloned offspring, the intent is to provide art taught reasoning as to why the instant claims do not appear to be enabled, why the specification fails to teach how to use the invention, and to illustrate the general state of the art in animal cloning and immunology to properly determine whether additional and specific guidance should be provided by the specification.

Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for the claimed invention. Although the instant specification provides a brief review of the general protocols for cloning an animal from lymphocytes, it is not enabled because it fails to teach how to overcome art known hurdles in reproductive cloning, particularly lymphocyte nuclear cloning, and it fails to provide any insight into the state of the immune system of a cloned animal compared to the founder, or reduce to practice to induce in any cloned animal any immune response that is substantially the same as the founder. Here, the general knowledge and levels of skill in the art do not supplement the omitted disclosure.

Therefore, in view of the limited guidance, the lack of predictability of the art and the nature of the claims, one skill in the art could not practice the invention without undue experimentation as it is now claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 provides a method for cloning a founder mammal, but the claim does not set forth any steps involved in the cloning process. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and

particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

Claim 1 also recites, "allowing said constructed clone to develop to maturity such that said immune response of said clone is identical to said immune response of said founder mammal". It is noted an immune response is a response of a subject to the stimulation of an antigen; and thus it is unclear how maturity relates to identical immune response.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave T. Nguyen** can be reached on 571-272-0731. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **William Phillips**, whose telephone number is (571) 272-0548.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Q. JANICE LI, M.D.
PRIMARY EXAMINER

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
March 6, 2006